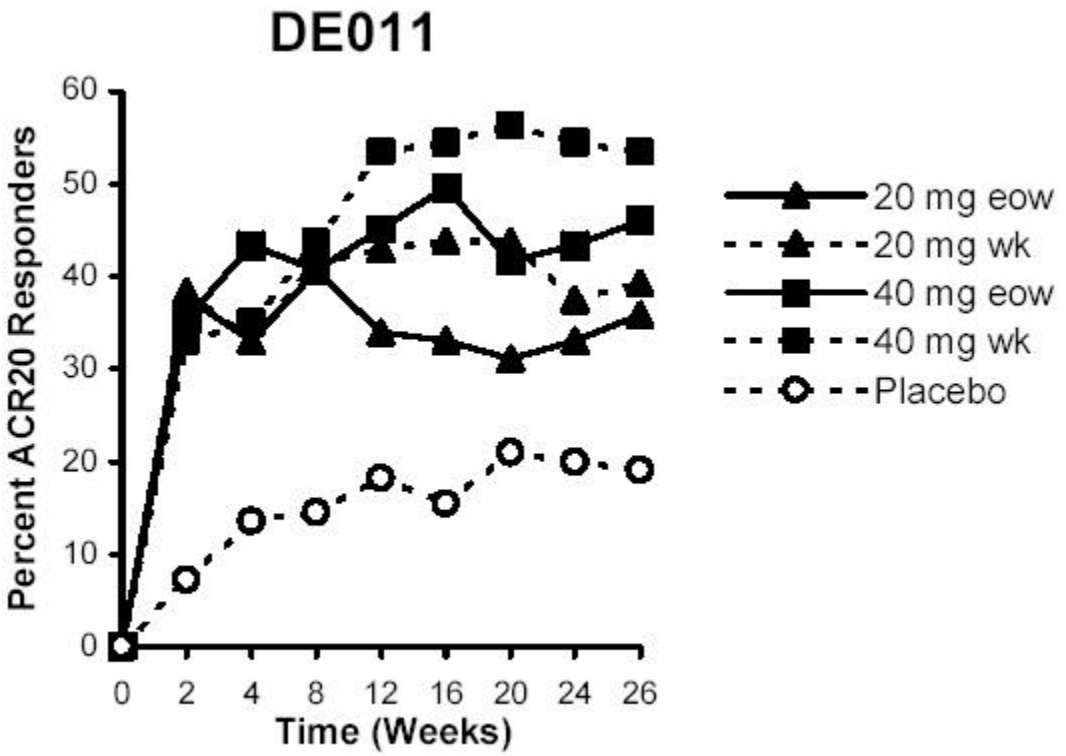

Figure 6 : Study DE011 : Responder rates according to ACR20 (observed values; full analysis set)

After 26 weeks of treatment, each of the four adalimumab treatment groups had higher ACR50, ACR70, and ACR-N responses than the placebo group. Statistically significant differences ($p = 0.05$) were observed for the recommended dose of adalimumab, 40 mg q2w, compared to placebo for the ACR20, ACR50 ACR70, and ACR-N responses (Table 9).

Table 9 : Study DE011 : Summary of Major Efficacy Results at Week 26 – Number and Percentage of Patients Responding By Randomized Treatment Group (full analysis set)

	Adalimumab				Placebo
	N=106	N=112	N=113	N=103	N=110
Efficacy Parameter	**20 mg eow**	**20 mg weekly**	**40 mg eow**	**40 mg weekly**	
ACR 20 response [o]	38/106 (33%)[a]	44/112 (38%)[a]	52/113 (**43%**)[a]	55/103 (**54%**)[abc]	21/110 (20%)
ACR 50 response [o]	20/106 (19%)[a]	23/112 (21%)[a]	25/113 (22%)[a]	36/103 (**35%**)[abcd]	9/110 (8%)
ACR 70 response [o]	9/106 (9%)[a]	11/112 (10%)[a]	14/113 (12%)[a]	19/103 (**18**%)[ab]	2/110 (2%)
	N Mean ± SD	N Mean ± SD	N Mean ± SD	N Mean ± SD	N Mean ± SD
ACR-N response [o]	N=68 25.6±37.5[a,f]	N=78 24.0±43.1[f]	N=82 26.7±44.4[a,f]	N=88 29.0±46.1[a,f]	N=48 8.3±52.6

[a] Statistically significant difference from placebo based on Pearson's x^2 test (p<0.05)
[b] Statistically significant difference from 20 mg q2w based on Pearson's x^2 test (p<0.05)
[c] Statistically significant difference from 20 mg weekly based on Pearson's x^2 test (p<0.05)
[d] Statistically significant difference from 40 mg q2w based on Pearson's x^2 test (p<0.05)
[f] Statistically significantly different from baseline based on 95% confidence intervals (p = 0.05).
[o] Observed values, means

Study DE011 provides baseline and LOCF Week 26 HAHA (human anti-human antibody, i.e., anti-adalimumab antibody levels) data for 432 monotherapy adalimumab-treated patients (no concomitant MTX), the largest number of single study patients evaluated for HAHAs. Twelve percent of patients in this study developed HAHAs. Among the adalimumab-treated patients, the ACR20 response is lower (nominal p= 0.0048) among the HAHA positive adalimumab-treated patients (26%) than among all the HAHA negative adalimumab-treated patients (46%). The ACR20 response is also lower (nominal p=0.104) at the proposed dosage of 40 mg biweekly among the HAHA positive adalimumab-treated patients (30%) than among the HAHA negative adalimumab-treated patients (50%) (Table 10).

Table 10 : Study DE011: Relationship between HAHA and ACR20 Response at Week 26

	HAHA Positive		HAHA Negative		P-value
	N	ACR20 (%)	N	ACR20 (%)	
All Patients	54	14 (26%)	488	196 (40%)	0. 0416
Adalimumab patients	54	14 (26%)	378	175 (46%)	0.0048
20 mg biweekly	19	7 (37%)	87	31 (35%)	0.921
20 mg weekly	11	1 (9%)	101	43 (43%)	0.048
40 mg biweekly	20	6 (30%)	92	46 (50%)	0.104
40 mg weekly	4	0 (0%)	98	55 (56%)	0.042
Placebo	0	0 (0%)	110	21 (19%)	----

Comparison of the dosing interval of adalimumab administration reveals a higher incidence of the development of HAHAs (nominal p = 0.0006) associated with biweekly administration (18%) compared to weekly administration (7%). To control for differences in overall dose, patients who received equal doses of adalimumab over a 2-week interval were compared, i.e. a weekly (20 mg qw) or a biweekly (40 mg q2w) injection. HAHAs were more common among the patients receiving the biweekly dosage(18%) than those receiving the weekly dosage (10%) (nominal p= 0.0816) (Table 11).

Table 11 : Study DE011 : Relationship of Dose and Dosing Interval of Adalimumab Administration and HAHA Development

	N	HAHA + (%)	P-value
All patients			
Weekly	214	15 (7%)	0.0006
Biweekly	218	39 (18%)	
Subgroup			
20 mg weekly	112	11 (10%)	0.0816
40 mg biweekly	112	20 (18%)	

3. Summary of Efficacy Data

In this trial, the ACR20 response at Week 26, the primary efficacy parameter, was shown to be statistically superior to placebo for all four adalimumab treatment groups. A dose-response relationship was observed for ACR20 response rates across the adalimumab treatment groups at Week 26, with the lowest response rate for the 20 mg q2w group (33%), and the highest response rate for the 40 mg weekly group (54%). The ACR20 response rate at Week 26 for the adalimumab 40 mg q2w treatment group (43%), the proposed approval dosage, was statistically superior to the placebo-treated group (20%). The majority of responders had achieved an ACR20 response by the Week 2 study visit, and separation between adalimumab-treated patients and placebo-treated patients continued through Week 26.

Among adalimumab-treated patients, biweekly administration of adalimumab resulted in a higher incidence of HAHA-positivity than weekly administration, and HAHA-positivity was associated with a reduced frequency of ACR20 responses.

IV. Study DE019 – Adalimumab Plus Background Stable Dose Methotrexate Trial

A. Clinical Trial Design

Study DE019 is a multicenter double-blind, randomized, placebo-controlled 52 week phase III trial of adalimumab add-on therapy to background methotrexate (MTX) conducted to investigate the efficacy, safety, immunogenicity, and effect on immune response of subcutaneous (sc) injections of adalimumab (20 mg weekly or 40 mg biweekly [q2w]) compared to placebo weekly in patients with active RA treated concomitantly with MTX. A secondary objective was to investigate the retardation of disease progression at 52 weeks as detected by x-ray. The trial is composed of three parts: 1) a washout period and 2) a 52-week double-blind placebo-controlled period conducted at 89 sites in the United States and Canada (Figure 7), and 3) a 52-week open-label period. Patients without an ACR20 response by Week 16 could receive rescue medication if requested by the patient and permitted by the investigator-physician. After completing the 52-week placebo-controlled treatment period, patients could enter a 52-week open-label period with every other week 40 mg adalimumab treatment. Results from the double-blind placebo-controlled period of this study (1-year) are presented in this report. The doses of 20 mg weekly and 40 mg eow were determined from the 12-week double-blinded period results of Study DE007.

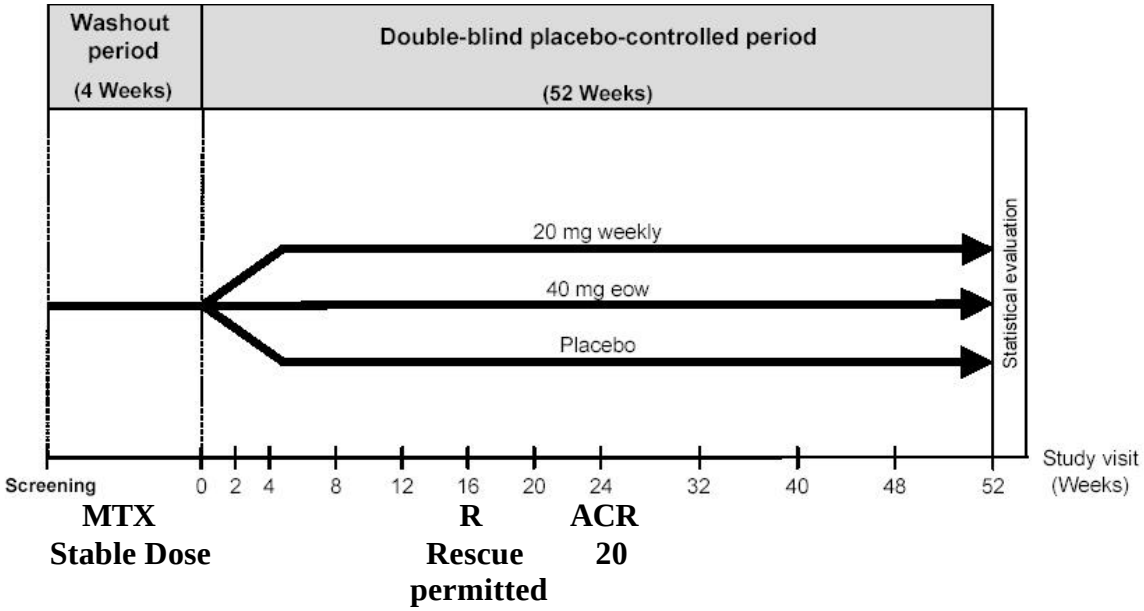

Figure 7 : Study DE019: Study Design of the 52-Week Placebo-Controlled Study

The planned sample size was 600 randomized patients with RA (as defined by the 1987 ACR criteria) who had been treated concomitantly with MTX for a minimum of 3 months, prior to study entry. Patients were screened for study eligibility based on the inclusion/exclusion criteria. At the baseline visit patients were randomized to one of three equal groups of 200 patients to receive one of three study treatments consisting of either adalimumab or placebo via subcutaneous injection for up to 52 weeks:

1. Weekly 20 mg adalimumab
2. Biweekly 40 mg adalimumab and on alternate weeks placebo
3. Weekly placebo.

Adalimumab or placebo was self-administered (or given by a qualified person) as a single sc injection (1.6 mL injectable solution in identical in appearance 2 mL. glass vials) every week or every other week for up to 52 weeks. The concentrations of adalimumab solution were 20 mg/1.6 mL and 40 mg/1.6 mL. Placebo solution was a buffered vehicle with Tween 80. Patients returned for periodic examinations at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52.

Eligibility consisted of RA patients with these inclusion criteria:

- Age 18 years and older, and for women of child-bearing potential demonstration of a negative pregnancy test (serum). .
- Met the ACR criteria for diagnosis of active RA and had at both the screening and baseline visits $\geq$ 6 swollen joints, $\geq$9 tender joints, and a C-reactive protein (CRP) $\geq$1 mg/dL, despite a minimum of 3 months of treatment with MTX.
- Taking a stable dose of MTX (oral, intramuscular, or sc) for at least 4 weeks prior to the screening visit with insufficient efficacy.

- Not taking DMARDs other than MTX (required a washout period during which all previous DMARDs [except MTX] were discontinued)
- Rheumatoid factor (RF) positivity or at least one joint erosion on x-ray. *[Based on changes made in Amendment B, patients were eligible if they had both RF positivity and a CRP $\geq$1 mg/dL, or at least one joint erosion on x-ray.]*
- Patients receiving stable daily glucocorticoids equivalent to $\leq$10 mg of prednisone

The dose of MTX was to remain constant during the 52-week double-blind period unless toxicity occurred.

The main exclusion criteria are evidence of cardiac, pulmonary, metabolic, renal, hepatic, gastrointestinal conditions, inflammatory joint or bowel disease, ongoing, recent, active, or latent infectious diseases, immune deficiency, history of lymphoma, leukemia or solid malignant tumor, history of tuberculosis or listeriosis, drug usage, alcohol abuse, recent joint surgery or injections, recent treatment with an investigational drug, laboratory values suggestive of possible MTX toxicity, having previously received any anti-TNF antagonist, pregnancy or breast-feeding.

At baseline and at every subsequent examination during the 52-week double-blind placebo-controlled period, joint assessments (tender and swollen joint counts) were performed by a blinded assessor, who was independent of the treating physician.

Study DE019 has three Primary Efficacy Endpoints:

1. Comparison of ACR20 response rates at week 24
2. Inhibition of radiographic progression at week 52
3. Disability index of HAQ at week 52

1) ACR20 response rates at Week 24 was the highest hierarchical primary efficacy outcome and was tested at the $\alpha = 0.05$ level of significance, Comparisons of responder rates were performed using Pearson's x^2 test per proposed analysis plan.

Observed data refers to patients with data available at the time point of analysis. Missing information for that time point, regardless of the reason, was not counted.

Observed data for ACR20 refers to patients with data available at the time point of analysis, but subjects were assessed as non-responder who:

- did not meet all of the ACR criteria on two consecutive visits at or after Week 12
- took additional DMARDs or increased MTX dose at or after the Week 16 assessments
- withdrew from the study prior to the measured time point (including ACR responders).

Comparisons were performed in sequence, using the closure principle to adjust for multiple comparisons. *[the first comparison was between ACR20 responder rates for*

all adalimumab-treated patients and placebo-treated patients, with subsequent comparisons between specific dose groups and placebo.]

2) Modified total Sharp x-ray score changes at Week 52 was the second hierarchical primary efficacy outcome. Radiographs of the hands/wrists and feet of each patient were obtained at screening and at Weeks 24, 52, and last visit for those who terminated early. The change in modified total Sharp x-ray score at Week 52 compared to baseline was designated as a primary endpoint. Digitized images of each radiograph were scored by two physicians (----------). The assessors were blinded to study treatment and the chronological order of the images. Missing values were imputed using linear extrapolation from baseline and the last during-study evaluation. A secondary analysis was performed following the LOCF approach to impute missing values. The difference among all treatment groups was to be assessed using analysis of covariance (ANCOVA) with the baseline value as the covariate.

The protocol specified that a Shapiro-Wilk test would be performed on the data to assess normality. If the results of the Shapiro-Wilk test indicated a non-normal distribution with a p value of = 0.05, the data were to be assessed using an analysis of ranks.

3) Disability index of the HAQ change at Week 52, the third primary efficacy endpoint was to be performed if the modified total Sharp x-ray score was significant at Week 52 (p = 0.05). The difference among all treatment groups was to be assessed using ANCOVA with the baseline value as the covariate. If this was significant (p = 0.05), pairwise comparisons between each active treatment group and placebo were to be evaluated using the same method.

Secondary efficacy variables consisted of classifying patients according to their level of improvement in disability index of the HAQ scores. Categories included an improvement of 0.22 (the minimally clinically significant change as defined by Goldsmith et al 1993) and 0.50 (considered a major improvement). This analysis utilizes LOCF approach for missing data.

Every effort was made to follow these patients and obtain x-rays even if they withdrew from the study.

B. Study Conduct

A total of 619 patients (approximately 200 per arm) were randomized and enrolled in the double-blinded, placebo-controlled period of this study at 89 sites in the United States and Canada in equal proportions in the three study arms (Figure 8). Approximately three-quarters of the patients completed the 52 week study, with a somewhat higher proportion completing in the adalimumab groups (78%) than in the placebo group (70%). A higher percentage of placebo-treated patients (30%) than adalimumab-treated patients (22%) withdrew early from the 52 week study. A higher proportion of patients discontinued treatment due to adverse events among adalimumab-treated patients (10%) than among placebo-treated patients (7%) (Table 12).

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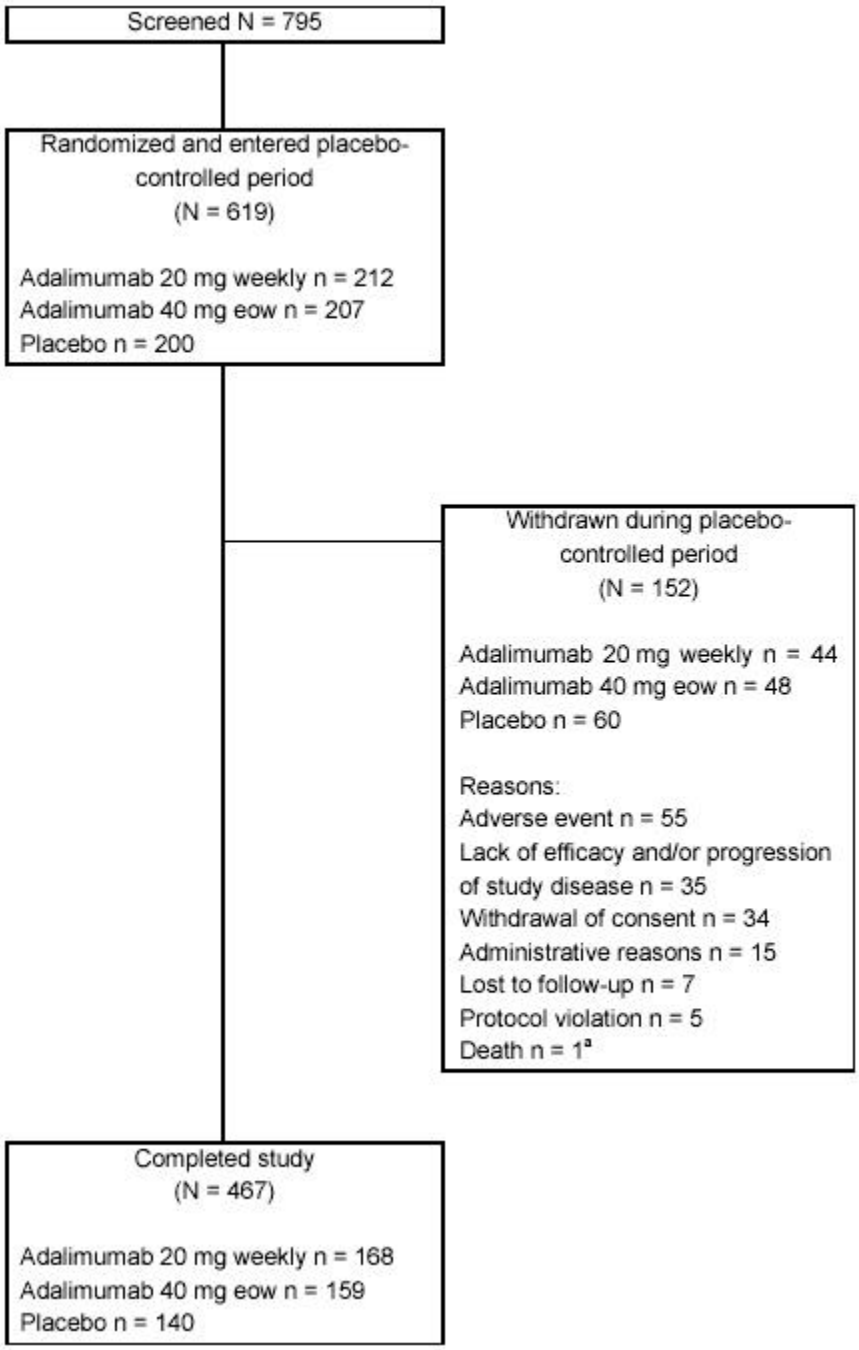


Figure 8 : Study DE019 : Patient Disposition

Table 12 : Study DE019 :Patient Disposition and Efficacy Assessment of Primary Endpoints At 24 and 52 Weeks

Planned enrollment N = 600	**Patients Screened N = 795**			
Enrolled & randomized	**N = 619**			
Completed study (52 weeks)	**N = 467**			
Withdrew early	**N = 152**			
Treatment	**Adalimumab**			
	20 mg Weekly N=212	**40 mg Q2W N=207**	**All Adalimumab N=419**	**Placebo N=200**
Completed study (24 weeks)	**181 (87%)**	**173 (85%)**	**354 (86%)**	**155 (78%)**
Withdrew early	**28 (13%)**	**32 (15%)**	**60 (14%)**	**45 (23%)**
Withdrawals from study:				
Adverse event	9 (4%)	17 (8%)	**26 (6%)**	**9 (5%)**
Withdrawal of consent	6 (3%)	5 (2%)	**11 (3%)**	**12 (6%)**
Lack of efficacy/progression of study disease	6 (3%)	5 (2%)	**11 (3%)**	**20 (10%)**
Administrative reasons	3 (1%)	0 (0%)	3 (1%)	2 (1%)
Lost to follow-up	3 (1%)	2 (1%)	3 (1%)	2 (1%)
Protocol violation	1 (<1%)	2 (1%)	3 (1%)	0 (0%)
Death	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)
Completed study (52 weeks)	**168 (79%)**	**159 (77%)**	**327 (78%)**	**140 (70%)**
Withdrew early	**44 (21%)**	**48 (23%)**	**92 (22%)**	**60 (30%)**
Withdrawals from study:				
Adverse event	16 (8%)	26 (13%)	42 (10%)	13 (7%)
Withdrawal of consent	11 (5%)	8 (4%)	19 (5%)	15 (8%)
Lack of efficacy/progression of study disease	6 (3%)	6 (3%)	12 (3%)	23 (12%)
Administrative reasons	5 (2%)	3 (1%)	8 (2%)	7 (4%)
Lost to follow-up	3 (1%)	2 (1%)	5 (1%)	2 (1%)
Protocol violation	3 (1%)	2 (1%)	5 (1%)	0 (0%)
Death	0 (0%)	1 (1%)	1 (0%)	0 (0%)

The demographic characteristics by randomized treatment group for all patients who entered the study demonstrated that the majority were Caucasians and three-quarters were females with a median age of 56 years, similar to other RA clinical trials. The demographic characteristics in the various groups were comparable at baseline. Participants manifested long-standing disease (medians 11 years) and active rheumatoid arthritis, as manifested by high mean TJCs (means 28) and SJCs (means all approximately 20) Over 75% of participants were RF positive. Mean baseline total Sharp scores were >66 and the disability index of HAQ was approximately 1.4. (Table 13 and Table 14).

Table 13 : Study DE019 : Demographic Characteristics

Treatment N = 619	Adalimumab			
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	Placebo N=200
Demographics				
Age (years) mean	**57.3**	**56.1**	**56.7**	**56.1**
Gender (female %)	**76**	**76**	**76**	**73**
Weight (Kg) mean	79.0	77.4	78.2	80.1
Height (cm) mean	166	165	165	166
Race (%)				
Caucasian	**85**	**84**	**85**	**83**
Hispanic	7	6	6	8
Black	6	7	6	7
Asian	1	2	2	1
Other	1	1	1	2

Table 14 : Study DE019 : Disease Activity Characteristics at Baseline

Treatment	Adalimumab			
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	Placebo N=200
Completed study	168 (79%)	159 (77%)	327 (78%)	140 (70%)
Duration of RA (years) - mean	**11**	**11**	**11**	**11**
Tender joint count - mean	**28**	**28**	**28**	**28**
Swollen joint count - mean	**20**	**19**	**20**	**19**
Total Sharp score - mean	**66.4**	**72.1**	**69.2**	**66.4**
Erosion score - mean	36.7	41.4	39.0	37.2
JS Narrowing score - mean	29.7	30.7	30.2	29.2
RF positive – number (%)	**165 (78%)**	**158 (76%)**	**323 (77%)**	**165 (83%)**
RF levels - mean	309	273	291	457
Disability index of HAQ-mean	**1.44**	**1.45**	**1.44**	**1.49**
Duration of morning stiffness minutes - mean	114	111	113	112

Previous DMARD therapy was comparable at baseline. The median total weekly dose of MTX was 15 mg/kg for both adalimumab-treated patients and placebo-treated patients and two-thirds of both groups received their medication via the oral route and one-third by the parenteral route (Table 15).

Table 15 : Study DE019 :Previous DMARD Therapy for Rheumatoid Arthritis

Treatment	Adalimumab			
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	Placebo N=200
Completed study	168 (79%)	159 (77%)	327 (78%)	140 (70%)
MTX Administration				
Route %				
Oral/ Parenteral	68/33	66/34	67/33	69/31
Total weekly dose - mg/kg (mean)	16.3	16.7	16.5	16.7

Eighty percent of patients enrolled in this trial contributed to the Week 24 evaluation of the ACR20. Over 90% of all study patients contributed to the Week 52 evaluation of decreased radiographic progression, and approximately 75% of all study patients contributed to the Week 52 Disability Index (HAQ) evaluation. Assessment of the data contributing to the efficacy primary endpoints is shown in (Table 16). More patients in the placebo-treated group (30%) withdrew from the trial than patients in the adalimumab-treatment groups (22%).

Table 16 : Study DE019 : Patients With Data Contributing To The Efficacy Assessments (Primary Endpoints)

Treatment	Adalimumab			Placebo
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	N=200
Completed study (52 weeks)	168 (79%)	159 (77%)	327 (78%)	140 (70%)
Withdrew early	44 (21%)	48 (23%)	92 (22%)	60 (30%)
ACR 20 at week 24	**181 (85%)**	**173(84%)**	**354 (84%)**	**155 (78%)**
Radiographic regression Sharp X-ray score changes				
Baseline enrollment	N = 201	N= 194	N = 395	N = 184
Scored at week 24	**196 (98%)**	**183 (94%)**	**379 (96%)**	**172 (93%)**
Scored at week 52	**196 (98%)**	**183 (94%)**	**379 (96%)**	**172 (93%)**
Disability Index (HAQ change)				
Baseline enrollment	N = 212	N = 206	N =418	N = 199
Observed score at week 52	**168 (79%)**	**160 (78%)**	**328 (78%)**	**140 (71%)**

C. Efficacy Analyses

1. Primary Efficacy Endpoints

The primary efficacy endpoints were 1) ACR20 response at Week 24, 2) change in modified total Sharp x-ray score at Week 52, and 3) change in disability index (HAQ) at Week 52 (Table 17). Statistically significant changes are demonstrated for all three primary efficacy endpoints.

Table 17 : Study DE019 : Primary Efficacy Assessments

Treatment	Adalimumab			
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	Placebo N=200
Completed study N =	168 (79%)	159 (77%)	327 (78%)	140 (70%)
Primary Efficacy Assessments				
ACR20 Response at week 24	**129 (61%)***	**131(63%)***	**260 (62%)**	**59 (30%)**
Radiographic progression - Change in modified Sharp X-ray score (erosions) at week 52				
N = at Week 52/Baseline	196/201	183/194	379/395	172/184
Baseline				
Mean ± SD	66 ± 56	72 ± 60		66 ± 47
Change at Week 52				
Mean ± SD	**0.8 ± 4.9 ***	**0.1 ± 4.8 ***		**2.7 ± 6.8**
Disability Index of the HAQ at week 52				
Baseline N =	212	206	418	199
Mean ± SD	1.44 ± 0.64	1.45 ± 0.63		1.48 ± 0.59
Week 52 N =	168	160	328	140
Change at week 52 ± SD	**-0.69 ± 0.55***	**-0.64 ± 0.57***		**-0.34 ± 0.54**
Additional Efficacy Assessment				
ACR20 Response at week 52	**116 (55%)***	**122 (59%)***	**238 (57%)**	**48 (24%)**

* Statistically significantly different from placebo ($p \leq 0.001$)

a. ACR20 Response at Week 24

An overall comparison of the change in ACR20 from baseline after 24 weeks of treatment revealed a statistically significant difference ($p \leq 0.001$) in each adalimumab treatment group (20 mg weekly [61%] and 40 mg q2w [63%]) compared to placebo [30%] (Table 17). The magnitude of the response at Week 24 was comparable between the 20 mg weekly and the 40 mg q2w treatments. Adalimumab-treated patients demonstrated statistically significant changes in all components of the ACR20 compared to placebo-treated patients (Table 18).

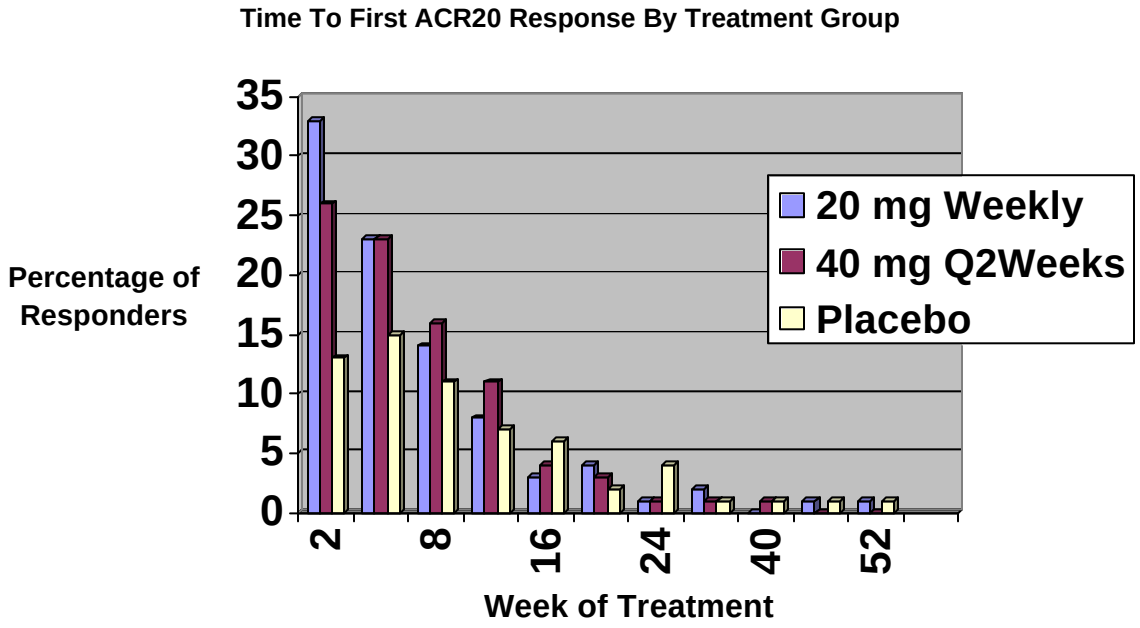
Table 18: Study DE019 :Components of ACR 20 Response Index (Percentage Change at Week 24 Compared to Baseline [a])

Efficacy Parameter	Adalimumab 40 mg q2w N = 207 (%)	Placebo N = 200 (%)
ACR 20 response at Week 24 [o]	63% ***	30%
TJC mean percent change [c]	63% ***	43%
SJC mean percent change [c]	61% ***	33%
1.Pain VAS [c]	62% ***	21%
2. Patient global assessment [c]	62% ***	23%
3. Physician global assessment [c]	70% ***	37%
4. HAQ Disability Index [c]	45% ***	16%
5. Acute phase reactant (C Reactive protein) [c]	50% ***	0
Duration of morning stiffness (minutes) [c]	83% ***	50%

* Comparison versus placebo (2-sided) p = 0.05.
** Comparison versus placebo (2-sided) p = 0.01.
*** Comparison versus placebo (2-sided) p = 0.001.
[a] Negative values indicate worsening
[o] Observed values; non-responders imputation; comparisons vs placebo by Pearson's chi-square test
[c] LOCF; ; Median percentage improvement -comparisons vs placebo by ANCOVA with factor treatment group and baseline value as covariate comparisons versus placebo (2-sided)

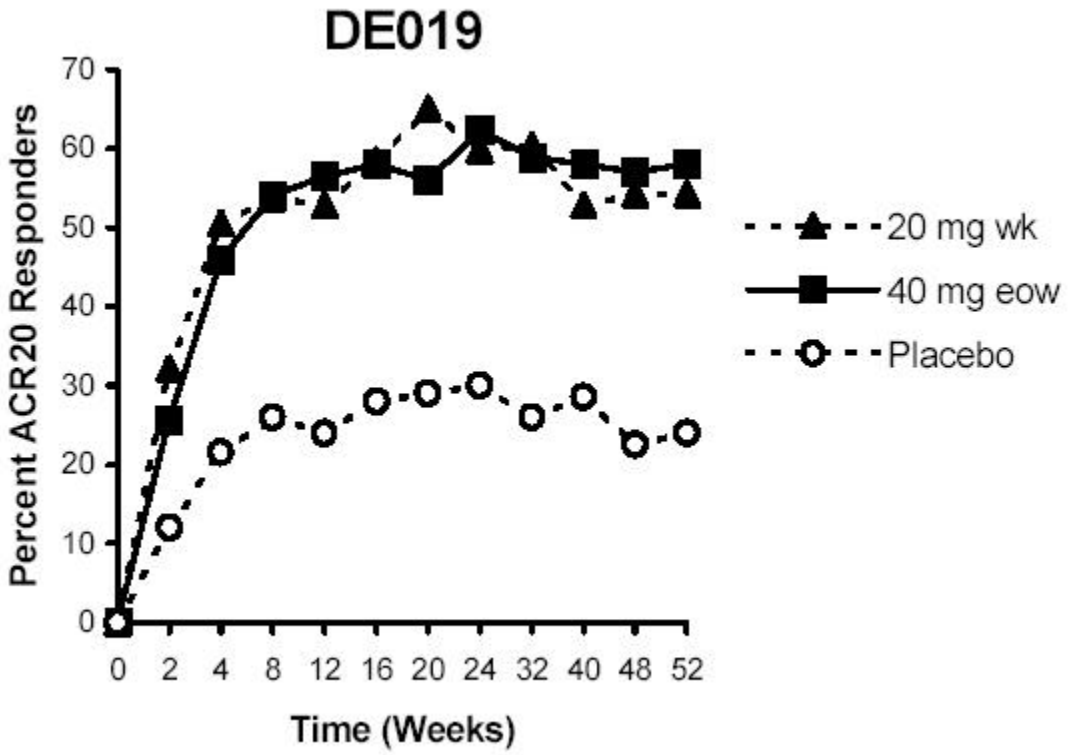
Evaluation of time to onset of ACR20 response by treatment groups demonstrates that the onset of action of adalimumab occurs as early as Week 2 with both dosages (Figure 9), and the majority of the adalimumab-associated ACR20 responses occur within the first eight weeks. Additionally, if an adalimumab treatment response is not observed by Week 20, the data suggest that an ACR20 response is unlikely to occur.

Figure 9 : Study DE019: Time to First ACR20 Response By Treatment Group



Overall, the adalimumab treatment groups had a higher response rate at each time point compared to placebo. Separation between adalimumab- and placebo-treated patients occurs as early as Week 2, is established by Week 4, and is maintained through Week 52 (Figure 10).

Figure 10 : Study DE019 : Percentage ACR20 Responders by Weeks



Evaluation of the maintenance of the ACR20 response at Week 52 (a secondary efficacy end-point) for adalimumab-treated patients who were responders at week 24, reveals that approximately 85% of early responders maintained their response through Week 52 compared to 63% for placebo-treated patients (Table 19).

Table 19 : Study DE019 : Maintenance of ACR20 Response at Week 52 For Patients Who Were Responders At Week 24 By Treatment Group

	Responders		
	Adalimumab		
	20 mg weekly (N=212)	40 mg q2w (N=207)	Placebo (N=200)
	N (%)	N (%)	N (%)
ACR20 Response at Week 24 (Based on all randomized patients)	**129 (61%)**	**131(63%)**	**59 (30%)**
ACR20 Response at Week 52 (Based on all randomized patients)			
Total	116 (55%)	122 (59%)	48 (25%)
Maintained from Week 24	**107 (51%)**	**117 (57%)**	**37 (19%)**
Not maintained from Week 24	9 (4%)	5 (2%)	11 (6%)
Percentage of Responders Maintained from Week 24 Through Week 52	**107/129 (83%)**	**117/131 (89%)**	**37/59 (63%)**

The percentage of ACR20 responses by treatment subsets among 40 mg q2w adalimumab-treated patients at Week 24 was uniformly greater than among placebo-treated patients with a few exceptions, i.e. among Blacks and Hispanics. Among the adequate and well-controlled groups, the ACR20 response for Blacks at Week 24 (36%, 11/31) resembled that for placebo (34%, 11/32). However, ACR20 responses among Blacks were higher than for placebo at six time-points earlier than Week 24 (Week 2 [39% vs. 13%], Week 4 [42% vs. 19%], Week 8 [52% vs. 28%], Week 12 [45% vs. 25%], Week 16 [48% vs. 31%], and Week 20 [39% vs. 31%]). In addition, comparison of the change in TSS (radiologic progression) between adalimumab- and placebo-treated patients revealed the highest rate of progression among Black placebo-treated patients (7.7u/yr) and a markedly reduced rate of progression among Black adalimumab-treated patients (0.4 u/yr) [Table 22]. Therefore, the data indicate that Black patients did have a response to adalimumab treatment. Patients subsetted based on weight, RF positivity, and corticosteroid use had similar responses to adalimumab (approximately 60%) as the study population as a whole (Table 20).

Table 20 : Study DE019 : ACR20 Responders at Week 24 by Treatment Subsets

	Adalimumab 40 mg Q2w		Placebo	
	N	%	N	%
Males	35	**71**	18	**33**
Females	96	**61**	41	**28**
Age				
< 65 years	93	**66**	48	**31**
= 65 years	42	**65**	13	**29**
Race				
White	111	**64**	39	**24**
Black	5	**36**	5	**39**
Asian	4	**80**	1	**50**
Hispanic	3	**23**	6	**40**
Other	1	**50**	1	**25**
Weight				
= 70 kg	56	**62**	14	**18**
= 70 kg	75	**64**	45	**37**
RF positive	110	**66**	54	**30**
RF negative	26	**67**	7	**33**
Corticosteroid use +	56	**62**	31	**31**

b. Modified Total Sharp X-ray Score Changes at Week 52

The rate of radiographic progression was evaluated by calculating the change in modified total Sharp x-ray scores (TSS)(relative to baseline) at Weeks 24 and 52. Missing data were imputed by linear extrapolation to week 52. An overall comparison of the change from baseline in modified total Sharp x-ray scores to Week 52 revealed a statistically significant difference ($p = 0.001$) across the treatment groups, and permitted pair-wise comparisons. Significance testing was to be done following the closure principle. The difference among all treatment groups was to be assessed using analysis of covariance (ANCOVA) with the baseline value as the covariate. Comparisons rates were performed using Pearson's x^2 test. The magnitude of the change associated with each of the adalimumab treatment groups was smaller and was statistically significantly different ($p = 0.001$ for both) from placebo (Table 21) indicating that adalimumab use was associated with a reduced rate of progression of structural damage.

Observed and LOCF (use of linear extrapolation to impute missing data) data demonstrated similar results. Similar results were observed when the data were analyzed using the per protocol set of patients. An overall comparison of the change from baseline in modified total Sharp x-ray scores to Week 52 for the per-protocol set revealed a statistically significant difference ($p = 0.001$) across the treatment groups, and permitted pair-wise comparisons. The magnitude of the change associated with each of the adalimumab treatment groups was smaller and was statistically significantly different ($p = 0.001$ for both) from placebo. The mean modified total Sharp score for the proposed adalimumab dose of 40 mg q2w at Week 52 was 0.1 compared to 0.8 for 20 mg qw and 2.7 for the placebo-treated patients.

Normality was evaluated by applying the Shapiro-Wilk test procedure to the residuals from the parametric model. The resulting p-value was = 0.05 indicating the normality assumption was violated. Therefore, the final analysis was performed following a non-parametric approach, ranking the results prior to fitting the model. Missing values were imputed using linear extrapolation from baseline and the last during-study evaluation.

Table 21 : Study DE019 : Modified Total Sharp X-Ray Score Changes (Extrapolated) At Weeks 24 and 52 By Treatment Group (full set analysis)

	Adalimumab											
	20 mg weekly				40 mg eow				Placebo			
Time point	N	Mean ± SD	Median	Range	N	Mean ± SD	Median	Range	N	Mean ± SD	Median	Range
Baseline	201	66.4 ± 56.3	48.5	(2.0-280.0)	194	72.1 ± 60.7	54.5	(1.5-308.5)	184	66.4 ± 47.4	55.5	(0.5-230.5)
Change at Week 24	196	0.6 ± 4.9 [a]	0.0	(-27.5-50.5)	183	0.3 ± 4.5 [b]	0.0	(-18.0-46.0)	172	1.3 ± 3.7	0.5	(-22.5-15.0)
Change at Week 52	196	0.8 ± 4.9 [b]	0.0	(-14.5-50.5)	183	0.1 ± 4.8 [b]	0.0	(-37.0-23.5)	172	2.7 ± 6.8	1.0	(-25.0-39.0)

[a] Statistically significantly different from placebo (p = 0.01) based on median values.
[b] Statistically significantly different from placebo (p = 0.01) based on median values

Modified total Sharp x-ray score changes are presented by subgroups in Table 22. Comparison of the changes between adalimumab-treated patients and placebo-treated patients demonstrates a smaller increase in modified total Sharp x-ray scores with adalimumab compared to placebo in each of the subgroup analyses with the exception of patients >65 years of age. Among patients > 65 years of age receiving 20 mg weekly, the 12-month change in TSS was similar to placebo (2.7 vs. 3.2 u/yr). However, in the group receiving 40 mg q2w, the 12-month change in TSS was reduced compared to placebo (1.6 vs. 3.2 u/yr).

Of note, the largest increase in radiographic progression occurred among Blacks taking placebo. However, the rate of progression was reduced to a similar level among Black patients receiving adalimumab as for other groups. Rheumatoid factor positivity or negativity did not seem to influence the effect of adalimumab on radiographic progression.

Table 22: Study DE019 : Modified Sharp X-Ray Score (Observed) Changes At Week 52 By Age, Gender, Body Weight, Race, and RF Status

Treatment	Adalimumab			Placebo
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	N=200
Completed study	168 (79%)	159 (77%)	327 (78%)	140 (70%)
Subgroup at Week 52	N / Mean ± SD			
Age				
< 65 years	**138** **0.3 ± 2.6**	**116** **-0.5 ± 4.8**	254	**128** **2.7 ± 7.1**
> 65 years	**45** **2.7 ± 8.8**	**49** **1.6 ± 4.8**		**33** **3.2 ± 5.5**
Gender (female) N= Change at week 52	138 1.0 ± 4.9	127 0.3 ± 4.7	265	116 2.9 ± 6.4
Body Weight				
≤ 70 Kg at Baseline N= Change at 52 weeks	62 0.8 ± 2.3	69 0.2 ± 6.0	131	59 3.8 ± 6.4
≥ 70 Kg at Baseline N= Change at 52 weeks	121 1.0 ± 5.9	96 0.1± 3.9	217	102 2.1± 6.9
Race (%)				
Caucasian	156 1.0 ± 5.4	143 0.1 ± 5.1	299	138 2.6 ± 6.9
Hispanic	11 0.0 ± 1.9	6 0.0 ± 0.8	17	10 0.9 ± 1.4
Black	11 0.7 ± 1.6	11 0.4 ± 4.0	22	8 7.7 ± 7.6
Asian	2 1.8 ± 1.1	4 0.3 ± 0.3	6	2 3.8 ± 5.3
Other	3 0.0 ± 0.0	1 -1.0	4	3 3.5 ± 4.1
Rheumatoid Factor (positive)				
Baseline N=	165	158	323	165
	68 ± 55.6	77.6 ± 61.3		68.5 ± 47.5
Change at Week 52 N=	149	135	282	145
	0.9 ± 5.2	0.0 ± 5.3		2.7 ± 6.4
Rheumatoid Factor (negative)				
Baseline N=	36	36	72	19
	58.9 ± 59.6	48.0 ± 52.6		48.2 ± 43.3
Change at Week 52 N=	34	30	64	16
	1.1 ± 4.1	0.5 ± 1.9		3.3 ± 9.8

As expected, the baseline TSSs were progressively higher in patients with increasing duration of RA. The overall therapeutic effect of adalimumab was similar at all stages of the disease (Table 23)

Table 23 : Study DE019 : Modified Total Sharp X-Ray Score (Observed) Changes At Week 52 By Duration of RA

Treatment	Adalimumab			
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	**Placebo** N=200
Completed study (52 weeks)	168 (79%)	159 (77%)	327 (78%)	140 (70%)
Withdrew early	44 (21%)	48 (23%)	92 (22%)	60 (30%)
Duration of RA				
0 –2 years				
Baseline N=	28	24	52	18
	21.7 ± 14.5	28.3 ± 27.4		25.9 ± 18.4
Change at Week 52 N=	24	24	48	15
	-0.0 ± 1.2	0.4 ± 4.1		4.7 ± 6.3
>2 – 5 years				
Baseline N=	37	42	79	43
	44.5 ± 38.1	36.3 ± 31.5		44.3 ± 37.1
Change at Week 52 N=	34	36	70	38
	1.5 ± 9.1	1.1 ± 2.4		3.9 ± 8.3
>5 – 10 years				
Baseline N=	48	42	90	41
	61.3 ± 44.9	51.9 ± 36.7		55.3 ± 39.0
Change at Week 52 N=	41	31	72	35
	-0.3 ± 3.4	-0.3 ± 3.9		2.3 ± 5.9
> 10 years				
Baseline N=	87	86	173	82
	93.3 ± 63.1	111.6 ± 63.9		92.4 ± 46.5
Change at Week 52 N=	83	74	157	73
	1.6 ± 3.9	-0.3 ± 6.2		2.0 ± 6.3

Source of Data: Sponsor's Table 25

The magnitude of the baseline TSSs did not have any apparent influence on the decrease in rate of progression of adalimumab-treated patients at the proposed dose compared to placebo-treated patients (Table 24).

Table 24 : Study DE019 : Modified Total Sharp X-Ray Score (Observed) Changes At Week 52 (Continued)

Treatment	Adalimumab			
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	Placebo N=200
Completed study (52 weeks)	168 (79%)	159 (77%)	327 (78%)	140 (70%)
Withdrew early	44 (21%)	48 (23%)	92 (22%)	60 (30%)
Baseline Sharp score				
Baseline score <30 N=	59	59	118	51
	16.0 ± 7.5	15.9 ± 7.0		16.4 ± 8.3
Change at Week 52 N=	52	53	105	44
	-0.0 ± 1.4	**0.5 ± 2.9**		**1.5 ± 3.3**
Baseline score 30 – 90 N=	91	81	172	75
	55.3 ± 16.9	58.7 ± 18.9		54.5 ± 16.5
Change at Week 52 N=	82	65	147	68
	1.2 ± 3.5	**-0.2 ± 5.4**		**4.1 ± 7.6**
Baseline score > 90 N=	51	54	105	58
	144.4 ± 51.6	153.6 ± 47.8		125.7 ± 28.2
Change at Week 52 N=	49	47	96	49
	1.5 ± 8.4	**0.1 ± 5.9**		**2.1 ± 7.6**

We performed analyses to determine what fraction of patients experienced no x-ray progression. At week 24, similar proportions of adalimumab-treated patients and placebo-treated patients manifested no new erosions. However at Week 52, 60% of the 40 mg q2w adalimumab-treated patients had no new erosions compared to baseline vs. 46% of placebo-treated patients (Table 25).

Table 25 : Study DE019 : Erosion Score: Patients with No New Erosions and Lower Erosion Scores at Weeks 24 and 52 by Randomized Treatment Group (full analysis set)

TimePoint	Adalimumab				Placebo	
	20 mg weekly		40 mg Q2w			
	N	%	N	%	N	%
Patients with no new erosions (=0 and <0)						
Week 24	117	62	108	**61**	99	**60**
LOCF Week 24	119	62	119	**62**	103	**58**
Week 52	106	58[a]	102	**62**[b]	74	**46**
LOCF Week 52	119	59[a]	122	**63**[c]	85	**46**
Patients with lower erosion scores (<0)[d]						
Week 24	59	31	65	**37**[a]	41	**25**
LOCF Week 24	60	31	69	**36**[a]	41	**23**
Week 52	54	30[a]	63	**38**[c]	31	**19**
LOCF Week 52	57	28[a]	72	**37**[c]	35	**19**

a Statistically significantly different from placebo (p = 0.05).
b Statistically significantly different from placebo (p = 0.01).
c Statistically significantly different from placebo (p = 0.001).
d Comparison was done across three categories: <0, 0 and >0.

Erosion score changes were greater for placebo-treated patients than for 40 mg biweekly adalimumab-treated patients at both Week 24 and Week 52, and changes for 20 mg weekly adalimumab-treated patients were intermediate. LOCF data demonstrated similar results (Table 26).